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(54) Title: RAPIDLY–SOLUBLE COMPOSITIONS

(57) Abstract

A composition in the form of a shaped body, comprises a rapidly soluble, open matrix of a carbohydrate polymer. Such a composition may be obtained by the removal of solvent from a solution containing the carbohydrate polymer and any other component(s), the solution being provided as a single dosage aliquot in a mould corresponding to the desired shape.

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RAPIDLY-SOLUBLE COMPOSITIONS

Field of the Invention

The present invention relates to rapidly-soluble compositions. The compositions are suitable for use as vehicles for the delivery, e.g. the mucosal or oral delivery, of bioactive substances. The compositions are also suitable for use as delivery vehicles for active substances requiring rapid release.

Background of the Invention

The most common pharmaceutical dosage form is the tablet. The main limitations of tablets are poor patient compliance due to the difficulty in swallowing tablets and the difficulty in achieving effective dissolution, to release the bioactive contents. Thus, there is a need for rapidly-soluble compositions. A number of approaches have been used, including effervescent tablets using a variety of volatile material-generating systems, chewable tablets, disintegrants and wicking agents.

More recently, therapeutic compositions have been formulated using rapidly-soluble matrices. These are especially useful for oral administration, such as for the lingual, sublingual or buccal delivery of drugs. The current most commercially popular form is described in US-A-4305502 and US-A-4754597, in which rapidly-soluble solid dosage forms are made by aliquoting a slurry of therapeutic agent, solvent, gelatin and other excipients into preformed depressions. The liquid is then frozen and the solvent removed by sublimation, typically freeze-drying. The resulting tablet has an open porous matrix that dissolves rapidly on contact with saliva at body temperature in the mouth. This dosage form, marketed by R.P.Scherer as Zydis®, has enjoyed commercial success, for instance, as in the Feldene Melt® tablets distributed by Pfizer.

This type of delivery vehicle allows rapid dissolution of the delivery vehicle on exposure to moisture. Consequently, the tablet dissolves almost immediately upon contact with mucosal surfaces. Although this format enjoys

a large market, it has the drawback of containing gelatin. Gelatin has the potential of contamination and is unsuitable for the treatment of vegetarians. The hygroscopicity of this gelatin formulation also means that Zydis® tablets have to be stored in moisture-resistant packs. The tablets quickly give rise to an unacceptable "sticky" mouth-feel resulting from the poor solubility of gelatin below 37°C, and accentuated by moisture uptake of the freeze-dried gelatin. Following buccal delivery, the mouth should not be washed out for 3-5 minutes.

EP-A-0357665 and US-A-4855326 describe therapeutic vehicles made from cotton candy. These have the advantages, of cost and simpler, more flexible processing, over Zydis® tablets. However, there are significant problems with the development of validated methods of compacting the candy floss into tablets and with the hygroscopicity of the tablets formed. Further, the tablets exhibit much slower dissolution than Zydis®, which precludes their use in buccal delivery formats which are possible with the latter.

US-A-4623394 discloses compressed tablets comprising pullulan and a gum-like heteromannan. The intention is to provide gradual disintegration. Even in a control experiment, without the heteromannan, the compressed tablet took over 2 hours to achieve 100% release.

Summary of the Invention

The present invention is based on the surprising discovery that pullulan or HES (hydroxyethyl starch) can satisfactorily be used as a replacement for gelatin, in tablets of the Zydis® type. This is despite the fact that attempts to use most carbohydrates and carbohydrate polymers, to form such matrices, including those proposed as potential substitutes for gelatin in the prior art, did not result in the production of tablets that were comparable to Zydis®. Pullulan (which is described herein by way of example only) provided instantaneous dissolution and stablility at ambient temperatures and humidities, thus

enabling its use in solid delivery forms as well as reducing the requirements and costs for water-resistant packaging for such delivery forms.

More particularly, it has been found that a rapidly soluble, open matrix of a carbohydrate polymer can be formed by removal of solvent from a solution containing the carbohydrate polymer and any other component(s), the solution being provided as a single dosage aliquot in a mould corresponding to the desired shape. It appears that materials such as pullulan can readily provide a shaped body that is not only readily invaded by water, but also low friability.

Description of the Invention

The present invention encompasses methods of making rapidly-soluble matrices of sugar (of which pullulan is an example, used herein for illustration) capable of dissolution in minimal volumes of aqueous solvent and of sufficient structural integrity to be handled as discrete units containing actives. These products are suitable for use in any applications that require fast-dissolving solid formulations. They are particularly suitable for use in mucosal delivery formulations, such as tablets for per-oral delivery, that dissolve in saliva.

In one embodiment, pullulan, any necessary or desirable excipients and active agent to be delivered are mixed in a liquid (in which one or more of the components may be soluble), frozen, e.g. in individual dosage aliquots, and then lyophilised, to remove the solvent and yield a rapidly-soluble matrix containing the active. The water or other solvent may also be removed by sublimation or evaporation. If desired, the liquid may be frozen as part of a continuous process of lyophilisation.

Products of the invention comprise matrices that are soluble not just at body temperatures but also at ambient and lower temperatures. They are thus suitable not just for oral or buccal delivery as solid matrices but also as soluble matrices for rapid dissolution in aqueous solvent

prior to administration. The latter formulations may be combined with other excipients and formulations that aid rapid disintegration and dissolution of solid matrices including effervescent couples.

A wide variety of bioactive materials are suitable for use in accordance with the present invention, including therapeutic and prophylactic agents. The delivery vehicle and methods of the present invention provide for a variety of dosing schemes for delivery of the bioactive material and are suitable for both veterinary and human applications.

Any suitable excipient may be used. Many examples will be well known to those skilled in the art. Criteria for the choice of excipients include their effects on the process for obtaining the rapidly-soluble matrix, or the physical or organoleptic characteristics of the matrix. For example, the product is a confectionery product and the excipients may include flavoring agents, food dyes, stabilisers and the like. Alternatively, the product is a therapeutic composition comprising pharmaceutical excipients as well as biologically active agents such as drugs.

Excipients suitable for use herein include other carbohydrates including sugars, sugar alcohols, straight-chain polyalcohols and non-reducing glycosides of polyhydroxy compounds. The preferred sugar alcohols are mannitol and xylitol. The glycosides are preferably monoglycosides, in particular the compounds obtained by reduction of disaccharides such as lactose, maltose, lactulose and maltulose. The glycosidic group is preferably a glucoside or a galactoside and the sugar alcohol is preferably sorbitol (glucitol). Examples include maltitol (4-O-β-D-glucopyranosyl-D-glucitol), lactitol (4-O-β-D-galactopyranosyl-D-glucitol), iso-maltulose, palatinit (a mixture of GPS, β α-D-glucopyranosyl-1→6-sorbitol, and GPM, α-D-glucopyranosyl-1→6-mannitol), and its individual sugar

alcohols, the components GPS and GPM. Suitable carbohydrates include, but are not limited to, lactose, αα,β,β and α,β-trehaloses, raffinose, palatinit, GPS, stachyose, mellibiose and mannotriose. In the case of a delivery vehicle, the excipients can include those found in confectionaries.

The presence of a low molecular weight carbohydrate, e.g. a mono-, di-, tri- or tetrasaccharide, can enhance the dissolution properties of a product of this invention.

The amount of therapeutic (or bioactive) agent should be suffficient to yield a final product that contains an effective amount of the therapeutic agent. The products obtained are suitable for use as pharmaceuticals, other medical applications such as diagnostics, environmental applications, agricultural and industrial use. An effective amount of a bioactive agent is one which causes amelioration or palliation of the condition to be treated. Such amounts are known in the art and readily determinable.

Examples of types of bioactive materials that can be used in the invention include any pharmaceutical agents, including anti-inflammatory drugs, analgesics, antiarthritic drugs, antispasmodics, anti-depressants, antipsychotics, tranquilisers, anti-anxiety drugs, narcotic antagonists, anti-Parkinsonism agents, cholinergic agonists, chemotherapeutic drugs, immunosuppressive agents, antiviral agents, antibiotic agents, appetite suppressants, antiemetics, anticholinergics, antihistaminics, anti-migraine agents, coronary, cerebral or peripheral vasodilators, hormonal agents, contraceptives, antithrombotic agents, diuretics, antihypertensive agents, cardiovascular drugs and opioids.

Suitable bioactive materials also include biological modifiers. Such modifiers include subcellular compositions, cells, bacteria, viruses and molecules including lipids, organics, proteins and peptides (synthetic and natural), peptide mimetics, hormones (peptide, steroid and corticosteroid), D and L amino acid polymers,

oligosaccharides, polysaccharides, nucleotides, oligonucleotides and nucleic acids, including DNA and RNA, protein-nucleic acid hybrids, small molecules and physiologically active analogues thereof. Further, the modifiers may be derived from natural sources or made by recombinant or synthetic means and include analogues, agonists and homologues.

As used herein "protein" refers also to peptides and polypeptides. Such proteins include enzymes, biopharmaceuticals, growth hormones, growth factors, insulin, monoclonal antibodies, interferons, interleukins and cytokines. Organics include pharmaceutically active chemicals with amino, imino and guanidino groups. Suitable steroid hormones include estrogen, progesterone, testosterone and physiologically active analogues thereof. Numerous steroid hormone analogues are known in the art and include estradiol, SH-135 and tamoxifen. Many steroid hormones such as progesterone, testosterone and analogues thereof are particularly suitable for use in the present invention as they are destroyed upon oral administration by the so-called hepatic first-pass mechanism. As used herein, "nucleic acids" includes any therapeutically effective nucleic acids known in the art including DNA, RNA and physiologically active analogues thereof. The nucleotides may encode single genes or may be any vector known in the art of recombinant DNA including plasmids, retroviruses and adeno-associated viruses. Preferably, the nucleotides are administered in the powder form of the solid dose vehicle.

Compositions containing prophylactic bioactive materials and carriers therefore are further encompassed by the invention. Preferred compositions include immunogens such as vaccines. Suitable vaccines include live and attenuated viruses, nucleotide vectors encoding antigens, heat-shock protein complexes, bacteria, antigens, antigens plus adjuvants, and haptens coupled to carriers. Particularly preferred are vaccines effective against

diphtheria, tetanus, pertussis, botulinum, cholera, Dengue, Hepatitis A, C and E, hemophilus influenza B, herpes virus, *Helicobacter pylori*, influenza, Japanese encephalitis, meningococci A, B and C, measles, mumps, papilloma virus, pneumococci, polio, rubella, rotavirus, respiratory syncytial virus, *Shigella*, tuberculosis, yellow fever and combinations thereof. Vaccines may also be produced by molecular biology techniques to produce recombinant peptides or fusion proteins containing one or more portions of a protein derived from a pathogen. For instance, fusion proteins containing the antigen of interest and the B subunit of cholera toxin have been shown to induce an immune response to the antigen of interest. See Sanchez *et al* (1989), Proc. Natl. Acad. Sci. USA 86:481-485.

Preferably, the immunogenic composition contains an amount of an adjuvant sufficient to enhance the immune response to the immunogen. Suitable adjuvants include aluminum salts, squalene mixtures (SAF-1), muramyl peptide, saponin derivatives, mycobacterium cell wall preparations, heat-shock proteins, monophosphoryl lipid A, mycolic acid derivatives, nonionic block copolymer surfactants, Quil A, cholera toxin B subunit, polyphosphazene and derivatives, and immunostimulating complexes (ISCOMs) such as those described by Takahashi *et al* (1990), Nature 344:873-875. For veterinary use and for the production of antibodies in animals, mitogenic components of Freund's adjuvant can be used. As with all immunogenic compositions, the immunologically effective amounts of the immunogens must be determined ertlpirically. Factors to be considered include the immunogenicity, whether or not the immunogen will be complexed with or covalently attached to an adjuvant or carrier protein or other carrier, route of administration and the number of immunising doses to be administered. Such factors are known in the vaccine art and it is well within the skill of immunologists to make such determinations without undue experimentation.

The present invention encompasses compositions and methods of making the compositions. Although singular forms may be used, more than one carbohydrate polymer and more than one excipient and active substance may be present. Determination of the effective amounts of these compounds is within the skill of one in the art.

Methods for lyophilising solutions to produce solid matrices are known in the art and have been described in, for example, US-A-4305502, US-A-4754597 and Rey et al (1975), Proc. R. Soc. Lond. B. Biol. Sci. 191:9-19. Conventional freeze-drying equipment can be used. Such equipment is commercially available, for example, from Edwards, FTS or Virtis. Alternatively, any equipment may be used that achieves the effect of producing freeze-dried products. Removal of solvent can be by sublimation and/or evaporation. For production of the rapidly-soluble solid matrices by lyophilisation, freezing can be carried out as a separate step or incorporated into the lyophilisation process. The exact processing conditions will be depend on the formulation and equipment and can be readily determined by one skilled in the art. Excipients may be added to enhance the processing and/or to tailor the physical or organoleptic properties of the compositions that are obtained.

The following Examples illustrate the invention.

Example 1

0.25, 0.5, 1 and 2.5% solutions of pullulan (PI-20, Hayashibara Co.) or HES in water containing 5% mannitol, raffinose or trehalose were dispensed into 1 ml aliquots into the wells of a plastic blister pack (Boots Ltd). The blisters were loaded into a Heto freeze-drier and frozen on the shelf held at -32°C before turning on the vacuum and lyophilising the frozen solution for 24 h (ramping from -20°C to 30°C) to yield a solid matrix of carbohydrate polymer plus sugar excipient. All the formulations used yielded intact solid matrices in the blister packs which dissolved instantaneously in water at room temperature

(15-20°C), even after a week's storage of the blisters on the bench at ambient temperatures and humidities. Only the matrices containing 1 or 2.5% carbohydrate polymer were of sufficiently low friability to be removed as an intact single dosage unit from the wells of the blister pack.

Example 2

Solutions containing 5% pullulan (PI 20, Hayashibara Co.), 5% mannitol and 20% dilitiazem (model hydrophilic active) were dispensed into 1 ml aliquots into the wells of a plastic blister pack (Boots Ltd). The blisters were flash-frozen at -70°C and then loaded into a Heto freeze-drier (shelf held at -10°C) and lyophilised for 4 h (ramping from -10°C to 60°C) to yield a solid matrix of carbohydrate polymer plus sugar excipient. The solid matrices in the blister packs were of sufficient non-friability (3.52%) to be removed as an intact single dosage unit from the wells of the blister pack and dissolved instantaneously in water (<2sec) at room temperature (15-20°C), even after a week's storage of the blisters on the bench at ambient temperatures and humidities. In comparison, the friability of commerical Zydis® tablets was 2.8% and the dissolution time c.8 sec. The mean water content of the solid matrices was 3.24% (SD 0.19%) and the mean content uniformity of active 98.62% (SD 0.73%).

Example 3

The procedure of Example 2 was repeated, but using, instead of diltiazem, 20% acyclovir (model hydrophobic active). The solid matrices obtained in the blister packs were of sufficient non-friability (2.69%) to be removed as an intact single dosage unit from the wells and dissolved instantaneously in water (<2sec) at room temperature (15-20°C), even after a week's storage of the blisters on the bench at ambient temperatures and humidities. The mean water content of the solid matrices was 4.75% (0.11%)and the mean content uniformity of active 105.63% (SD 0.96%).

Although the foregoing invention has been described in some detail by way of illustration and example for purposes

of clarity of understanding, it will be apparent to those skilled in the art that certain changes and modifications may be practised. Therefore, the description and examples should not be construed as limiting the scope of the invention, which is delineated by the appended claims.

CLAIMS

1. A composition in the form of a shaped body, comprising a rapidly soluble, open matrix of a carbohydrate polymer.

2. A composition according to claim 1, wherein the carbohydrate polymer is hydroxyethyl starch.

3. A composition according to claim 1, wherein the carbohydrate polymer is pullulan.

4. A composition according to any preceding claim, which comprises at least one excipient.

5. A composition according to any preceding claim, which comprises a low molecular weight carbohydrate.

6. A composition according to any preceding claim, which comprises a component selected from colouring agents and flavouring agents.

7. A composition according to any preceding claim, which comprises a therapeutic agent.

8. A composition according to any preceding claim, in the shape of a tablet.

9. A composition according to any preceding claim, obtainable by the removal of solvent from a solution containing the carbohydrate polymer and any other component(s), the solution being provided as a single dosage aliquot in a mould corresponding to the desired shape.

10. A composition according to claim 9, wherein the removal of solvent comprises freeze-drying.

INTERNATIONAL SEARCH REPORT

Intl. Ional Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 40077 A (GRIBBON ENDA MARTIN ;QUADRANT HOLDINGS CAMBRIDGE (GB); ROSER BRUCE) 19 December 1996 (1996-12-19) page 3, line 12 - line 22 page 4, line 22 - line 26 figure 2 page 7, line 3 - line 17 page 27, line 6 - line 18 claim 1	1,2,4-9
X	WO 91 09591 A (MEDIVENTURES INC) 11 July 1991 (1991-07-11) page 7, line 1 -page 8, line 41 page 34 -page 45; examples 19-30 claims 1-4	1,4-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Inte. .onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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